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PYELONEPHRITIS—ITS NATURAL HISTORY AND COURSE[1]

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INTRODUCTION

There are two major and broad problems in bacterial infection that face us today. They are the control of staphylococcic infections and the control of cases of bacillary sepsis. Staphylococcic infections that are resistant to all existing forms of chemotherapy are prevalent in hospital patients and are particularly common in wound infections. Bacillary sepsis makes its greatest impact in urinary tract infections and they too are common in hospital patients. Pyelonephritis, acute and recurrent, active and healing, as well as healed, is the number one problem in infectious disease due to bacteria today and demands continuing attention and intensive study. It is a problem calling for a high priority of investigation. These cases are increasing in frequency.

During the past 25 years, there have been a tremendous number of studies dealing with all of the problems encountered in urinary tract infections. The studies received new stimulus with the development of many new antiinfective agents, the recognition that a certain number of patients with unilateral pyelonephritis and a contracted kidney have hypertension that can be relieved by nephrectomy, and finally the recognition of the fact that chronic bilateral pyelonephritis with contracted kidney, with or without an associated hypertension, is the commonest cause of uremia.

Further, since pyelonephritis is an infection that tends to be recurrent and chronic, there is always the hope that we may be able to prevent it. If that is impossible, we may at least be able to keep it from becoming chronic or progressive, causing prolonged suffering and death.

How does pyelonephritis look when pinned out in the physician's collection? There seem to be two basic problems: first, how to prevent renal tract infections, especially recurrent infections; and second, how to manage them most effectively when they do occur. Our knowledge is incomplete. There is a great need for more fundamental information concerning all bacillary infections and how they are controlled in the human body. However, by reviewing our present knowledge, new light may be shed on the problems that command attention.

[1] Lecture I of the twenty-second course of lectures under the William Sydney Thayer and Susan Read Thayer Lectureship in Clinical Medicine. Delivered at The Johns Hopkins Hospital April 26, 1956.

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VITAL STATISTICS

Inasmuch as pyelonephritis is such a common disease, a large number of facts have developed concerning it. A few may be outlined as follows.

1. Pyelonephritis occurs most commonly at three age periods: a) during infancy and childhood, b) during the childbearing period, and c) during the aging process associated with lower urinary tract obstruction or with other diseases of the kidney in the elderly.

2. Pyelonephritis is a more frequent cause of Bright's disease than is chronic glomerulonephritis at all ages, and it is the commonest renal lesion in uremia. Further, acute exacerbations of pyelonephritis are considered to be a common precipitating factor in uremia, when the disease has been latent or when other forms of Bright's disease are present.

3. Pyelonephritis is not infrequently associated with hypertension, especially in those under 50 years of age and particularly under 40 years. It is associated with "malignant hypertension" in between 15 and 20 per cent of all cases. In Longcope's cases (1) of pyelonephritis, hypertension was an associated feature in half of them. In all carefully studied cases of hypertension, pyelonephritis is present in about 20 per cent.

4. In infancy and childhood, the association with congenital abnormalities is frequent (50 to 70 per cent of cases).

5. This is the commonest renal lesion found at necropsy and is present in 15 to 20 per cent of all autopsies, regardless of the cause of death. It is of major importance as a cause of death in about one-third of the cases (2 to 5 per cent of all autopsies), and only incidental, latent or contributory in the other two-thirds.

6. Diabetic patients show pyelonephritis about four times as often as nondiabetics.

7. Renal infections are one of the common complications of pregnancy and to a lesser extent of the puerperium. They are present in about 20 per cent of the cases of toxemia of pregnancy.

8. Aside from the frequency of pyelonephritis in diabetes, it is seen in association with renal calculi, renal tumors, and obstructions of the lower urinary tract, including disturbances in the innervation of the bladder.

9. The disease may be unilateral or bilateral. It may run a rapidly progressive course ending in death, or it may heal completely with resumption of normal renal function. It may run a chronic progressive course with exacerbations and remissions over a period of 1 to 20 years, the patient finally dying in uremia or with heart failure.

ACUTE PYELONEPHRITIS

Acute pyelonephritis may be unilateral or bilateral, and the route of infection may be hematogenous or lymphogenous, or the disease may ascend from the

TABLE I

Etiology of Urinary Tract Infections

Bacillary infections	
E. coli	188
Ae. aerogenes	48
B. proteus	27
Ps. aeruginosa	56
B. faecalis alcaligenes	5
H. influenzae	1
Coccal infections	
Staphylococci	46
Enterococci	7
Mixed infections	
Mixed infections (bacillary)	57
Mixed infections (coccal)	3
Mixed infections (coccal and bacillary)	39
	477

lower urinary tract through the ureters. Regardless of the route of infection, acute pyelonephritis is primarily a disease of the interstitial tissues of the kidney, with varying degrees of involvement of the tubules. Experimental production of acute pyelonephritis in animals and the examination of the kidneys in man disclose enlargement of the kidneys, small abscesses in the pyramids and cortex, tubules distended with pus, and infiltration of leukocytes in the intertubular connective tissue.

Bacteria are found in the interstitial tissues, in the tubules, and in the perivascular lymphatics, and there may be acute inflammation of the arterioles and venules with fibrin formation in the wall and thrombosis. The glomerulus and the periglomerular lymphatics are also inflamed.

Etiology—microörganisms

The development of antiinfective agents has emphasized the importance of studying the bacterial flora of urinary tract infections with great care, because the selection of therapy will depend in part on the species of organism present in the urine.

The two commonest organisms isolated from single-type infections are *Escherichia coli* and *Staphylococcus aureus*. The other common Gram-negative organisms that cause pyelonephritis in declining frequency are *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, and *Proteus vulgaris*. Aside from staphylococci, enterococci are the commonest Gram-positive microörganisms found in the urine. (Table I lists the common and uncommon microörganisms found in the urine, based on our experience with 477 patients.) General experience agreeing with our own indicates that between 75 and 80 per cent of urinary tract infections are bacillary in origin and 20 to 25 per cent are coccal in origin.

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In our experience with the last 600 cases, 74 per cent of acute bacillary infections were caused by a single organism in the acute phase of the infection. Once a patient has been treated with an antibiotic or has required an inlying catheter or an operation on the urinary tract, the infection is likely to become mixed. Also a mixed infection may be present in a complicated urinary tract lesion.

SPECIFIC TYPES OF PYELONEPHRITIS

Staphylococcus

Staphylococcic sepsis is associated with metastases in the kidney in 20 to 40 per cent of cases. The renal lesions may be focal or diffuse and may lead to single abscesses or to multiple small abscesses. They may extend beyond the kidney to the perirenal space. They may heal or may become chronic and lead to chronic pyuria or stone formation.

In the experience of Nesbit and Dick (2), acute staphylococcic infection of the kidney is hematogenous in origin and the lesions are cortical in location. There is a tendency for healing to take place promptly and completely. Fever, costovertebral tenderness, and pain are constant features. Characteristically, the urine contains very few leukocytes during the acute stage of the disease, but the stained sediment reveals the presence of many staphylococci. In their experience, the disease tends to run an acute and self-limited course over a ten-day to two-week period and ends in complete recovery in 90 per cent of cases. The commonest complication is perirenal suppuration. Chronic pyelonephritis is not a problem in this type of infection.

Hemophilus influenzae

Albright, Dienes and Sulkowitch (3) were the first to describe two cases of subacute pyelonephritis associated with *H. influenzae* in a strongly alkaline urine. Roentgen ray examination of the kidney showed a diffuse nephrocalcinosis. Temporary sterilization of the urine followed the use of sulfanilamide. Infections of the urine due to this organism have been described by others but nephrocalcinosis has not been a feature of the infection.

Streptococcus

Streptococcal organisms are isolated from the urine in many cases of urinary tract infection. They are usually Group B or D of Lancefield. The infections are usually mild, but occasionally serious. They are seen most often in obstruction to urinary flow, in cystitis, and following catheterization in women.

Proteus, Pseudomonas, Aerobacter

These organisms are found most often in mixed infections and when there are complicated or structural abnormalities of the urinary tract, particularly

those that have occurred following instrumentation, catheterization, or prior antibacterial therapy.

The examination of the urine for bacteria should be carried out on a quantitative basis and with the use of Gram stain of a *freshly collected* and *unsedimented* urine. Kass (4) has reported recently that organisms are readily found in stained specimens of urine when about 10^5 bacteria or more are present in the urine. The quantitative study of freshly voided specimens of urine for bacteria by the dilution method, first advocated in my experience by Bloomfield in this clinic, is most important in attempting to discriminate between contamination and actual infection. In a quantitative study of microörganisms in the urine of patients with pyelonephritis by Rantz and myself (5), we found that 10^{5-6} or more organisms per milliliter of freshly voided and promptly cultured urine were always present during acute infections.

Kass studied this question further and found that when *acute pyelonephritis* was present, the bladder urine of a freshly voided specimen always contained more than 100,000 bacteria per milliliter. He made the additional further important observation that urine obtained from the kidneys of patients with acute pyelonephritis often contained fewer than 10,000 bacteria per milliliter, whereas the bladder urine at the same time often contained as many as 10^8, indicating that the bacteria multiply in the bladder urine.

Moreover, from a study of bladder urine obtained from patients without evidence of pyelonephritis, Kass found the urine to be sterile in 25 per cent of cases, to contain less than 100 bacteria in 40 per cent, and to contain less than 1000 bacteria in about 30 per cent. He has concluded from these studies that bacterial counts of 10^5 or more per milliliter of urine are probably significant of infection, and that counts significantly lower than this probably represent contamination. While there are limitations in the use of this information, it is useful if one takes into account the rate of urine flow, the presence of a bacteriostatic agent and the pH and dilution of the urine at the time it is examined.

The identification of the infecting microörganisms and the determination of the intensity of the infection should be followed by a study of the sensitivity of the organisms to various antiinfective agents for the purpose of planning optimum chemotherapy.

There is general agreement, then, that *E. coli* and *Staph. aureus* are the two organisms most often present in acute urinary tract infections, and that *Proteus*, *Pseudomonas* and *enterococcus* are more common in chronic and anatomically complicated infections than in uncomplicated infections. *Enterococci* are found most often in women following catheterization. Cultures containing more than one species are usually indicative of chronic or complicated infections.

It is exceedingly important to identify the bacteria in the urine and test their sensitivity to antibiotics. But what is more important for the long range is to

TABLE II

Associated Anatomical and Etiological Factors in 94 Fatal Cases of Pyelonephritis

Hematogenous infection without obstruction	26
Benign prostatic hypertrophy	16
Renal calculi	18
Cancer of prostate	6
Cord bladder	5
Urethral stricture	5
Cancer of cervix	5
Cystitis	5
Associated chronic vascular disease of kidney	8
	94

make more studies of how bacilli are killed in the human body in order to determine what part blood plasma antibody plays and what part intracellular destruction plays. It is well to remember that many bacilli enter tissue cells and survive there for long periods of time in spite of a high concentration of antibody or antibiotic in the surrounding medium. Bacilli living within cells may be protected and may account for persisting and recurrent infections.

PREDISPOSING FACTS AND PATHOGENESIS

Acute pyelonephritis is observed at all ages, but it has three major peaks of incidence, the first in infancy and childhood, the second during the childbearing period and the third in the elderly when urinary tract obstructions are common. The kidney may be infected following a bacteremia arising from an extra renal focus, or following the stasis of urine. Further, it shows a high incidence of infections in people with chronic disease such as diabetes. In infants and children, it is well to look for signs of congenital abnormalities when signs of acute pyelonephritis are present, and to bear in mind that 10 per cent of cases are unilateral in origin or predominantly unilateral. In young adults, important predisposing factors are catheterization, spinal anesthesia with urinary retention followed by catheterization, obstruction of the urethra, pregnancy, stone and late congenital defects such as congenital cystic kidneys, congenital and familial interstitial nephritis, and hypoplastic kidneys.

In the elderly, benign prostatic hypertrophy and cancer of the prostate in males and diabetes and cystitis in females are common predisposing factors.

In the last 94 fatal cases of acute pyelonephritis that I have observed at necropsy, the distribution of cases was as listed in Table II.

One of the curious features about both acute and chronic pyelonephritis is the fact that the disorder is caused most often by microörganisms that live normally in the gastrointestinal tract, although after antibiotic therapy they may be found in the mouth, throat, and respiratory passages, and when there

is a chronic draining sinus, such as occurs in chronic otitis media, *E. coli* and other intestinal bacteria are not infrequently present.

We are almost totally ignorant about the biological factors that favor the localization and growth of bacteria in various organs of the body. However, we can admit that the kidney is the one organ where microörganisms which ordinarily adapt themselves to the intestinal tract and live a parasitic existence may focalize, reproduce and damage tissue. Such factors as an increase in the hydrostatic pressure within the kidney, stasis, and obstruction to the free flow of urine, even within the renal tubules and perivascular lymphatics, favor the growth and persistence of organisms in some mysterious way. We need to know more about the biochemical factors of bacteria as well as the chemical factors of the kidney itself before we can go much further in understanding the problems of localization of organisms in the kidneys.

DIABETES

Urinary tract infections occur frequently as a complication of diabetes (Sharkey & Root, Kass). The symptoms referable to the kidneys are frequently absent or latent. Acute renal tract infections in diabetic patients are often precipitated by catheterization, and the tendency of these infections to recur and become chronic is common. Medullary or papillary necrosis or necrotic papillitis is found most often in diabetic patients, and there is often an associated vascular disease of intercapillary glomerulosclerosis. Kass (4) has recently reported that pyelonephritis occurs about four times as often in diabetics as in non-diabetics who come to necropsy, and that the kidney disease often remains latent and undetected during life. In the fatal cases of diabetes reported by Sharkey & Root (6) some years ago, 18 per cent had signs of urinary tract infection at necropsy and 70 per cent were secondary to infection elsewhere in the body.

Appreciating the high incidence of infection in diabetic patients and the common occurrence of urinary tract infections in these people should lead one to take all possible precautions against infection, and particularly against introducing infection into the genitourinary tract, because infection of the kidney may result in generalized sepsis, in coma, in renal insufficiency, uremia and death. This is true of necrotizing renal papillitis or necrosis of renal papillae, a form of acute pyelonephritis.

NECROSIS OF RENAL PAPILLAE

Although von Friedrich 79 years ago described necrosis of the renal papillae associated with hydronephrosis in a man aged 70 years with prostatic hypertrophy, it remained for Günther (7), 50 years later, to direct attention to the triad of pyelonephritis, necrosis of the renal papillae, and diabetes mellitus. Günther recognized that necrosis of the papillae occurred in non-diabetic

patients with pyelonephritis, especially when there was some obstruction to the free flow of urine in the lower urinary tract, but eight of the 10 specimens described by him were from patients with diabetes. Since the appearance of Günther's paper 19 years ago, a number of excellent studies and reviews of this subject have been made, and gradually more and more physicians are beginning to recognize this serious anatomical form of pyelonephritis.

The highlights of this disease are as follows. This form of acute pyelonephritis often accompanies diffuse pyelonephritis involving the cortex as well as the medulla, but the cortex may be free of abscesses in at least a third of the cases. It is seen most often in diabetic patients or in those with obstruction of the lower urinary tract in the age period of 50 to 80 years. The lesion may be unilateral or bilateral. It is observed in both sexes, men predominating for lower urinary tract obstruction and women for diabetes and non-obstructive lesions.

A variety of bacteria have been implicated as etiologic agents, but the three most commonly encountered organisms have been *Staph. aureus*, *E. coli* and *P. vulgaris*. Similar anatomical lesions have been observed in tuberculosis of the kidney and in rare instances of actinomycosis. A study of this form of pyelonephritis provides us with important information about the pathogenesis of renal disease.

PATHOLOGY

The gross description of the kidney shows two main features: 1) a readily recognized, pale yellow-white, infarct-like necrosis of the papillae, and 2) a green to red zone of inflammatory reaction extending around the involved pyramid but usually not reaching the arcuate artery. A more minute description of the lesions has been given by Robbins, Mallory and Kinney (8), Edmondson, Martin and Evans (9), Sheehan (10).

Briefly, the earliest lesions begin as abscesses in the interstitial tissues or perhaps in obstructed tubules of the pyramids. These abscesses enlarge and become confluent, so that a small area of infarct necrosis develops distal to the area involved and spreads almost to the tip of the papilla. Robbins, Mallory and Kinney explain the character and distribution of the lesion by an interference of the circulation in the pyramid. In the normal kidney, no blood vessels larger than capillaries are found in the distal two-thirds of the pyramid, and its entire blood supply consists of medullary arterial capillaries arising from the arterial rectae and descending into the distal two-thirds of the pyramid. The entire blood supply of the pyramid consists of arterial capillaries leading down and venous capillaries leading up the pyramid. The anatomic connections between the blood vessels of the cortex and medulla are poorly developed, so that inflammatory lesions in the pyramids can hinder the afferent blood supply and cause infarction and necrosis.

In the well developed lesion, the entire papillae are necrotic. The capillaries, tubules, lumen and interstitial tissues contain masses of microörganisms and are surrounded by polymorphonuclear leukocytes. Some capillaries contain fibrin and thrombin, and above the obstruction the capillaries are engorged and dilated. Extensive thrombophlebitis of the venous system is noted in some cases.

In the zone of red-green inflammation, which extends around the complete periphery of the involved pyramid, no organisms or capillary thrombi are visible. The central portions of the papilla show infarct necrosis but maintenance of normal architecture with little or no inflammatory reaction.

This stage of acute necrosis is followed in some cases by sequestration of the papillae so that they are cast off. In rare cases, after sloughing occurs the base of the area heals.

In short, the principal lesion is an infarct-like necrosis extending from the papillae upward into the pyramid. There is obstruction of the blood supply and a sharp border of inflammatory tissue without necrosis. Sequestration follows and healing rarely occurs.

CLINICAL FEATURES

It is well to remember that the candidates for this type of pyelonephritis are patients with diabetes and pyelonephritis and men with lower urinary tract obstruction. Precipitating factors that may aggravate or incite infection are the use of in-lying catheters or instrumentation.

This form of the disease should be suspected in a diabetic patient or a person with lower urinary tract infection when there is a sudden increase in symptoms and signs of infection, chills, fever, back pain, pyuria, the occurrence of massive hematuria, unilateral colic or an unexplained comatose state, or a rapidly rising nitrogen retention with oliguria or anuria, or bacteremia. Pyuria may be of only short duration prior to exacerbation of the disease. Urinary output may be normal.

The diagnosis may be suspected further by retrograde pyelography which shows 1) deformity of the tip of the calyx with narrowing of the neck by separated particles and peripheral excavations extending into the cortex, 2) shadows corresponding to the necrotic papillae, 3) sloughing of tips which appear as free masses in the renal pelvis, and 4) replacement of the concave tip of the calyx by dilatation, suggesting a cavity.

In view of the high incidence of this disease in diabetes, everything possible should be done to prevent it. If it occurs, it should be decided as promptly as possible whether it is unilateral or bilateral, since unilateral disease is treated in some cases by nephrectomy. Since the organisms that cause the disease are often sensitive to antibiotics, they should be identified, their sensitivity determined and active treatment started at once. When unilateral, nephrectomy may be curative.

PYELONEPHRITIS OF INFANCY AND CHILDHOOD

Pyelonephritis of infancy and childhood is one of the most important infections occurring in this period of life. It is associated with congenital abnormalities of the urinary tract. It may be acute or chronic, unilateral or bilateral. Patients with pyelonephritis during this age period may recover with no impairment of renal function, or they may die during the acute phase of their illness. They may recover and have latent pyelonephritis with impairment of function and a decreased renal reserve, or they may have an intermittent and recurrent or progressive infection with a healing or healed pyelonephritis and renal insufficiency that leads to uremia, hypertension and renal dwarfism or all three.

It is well to concentrate attention on pyelonephritis of infancy and childhood because it is in this age period that chronic disease begins, and it is also the age when infections most frequently cause premature death and protracted illness.

While congenital abnormalities of the urinary tract were considered to be important in the pathogenesis of pyelonephritis of infancy and childhood for a long period, it remained for Bugbee and Wollstein (11) to bring the subject into sharp focus in 1924. In reviewing 4903 necropsies, they found 117 infants, or about 2 per cent, with congenital abnormalities of the urinary tract. Observations made since then by Helmholz (12), Campbell (13), Butler and Lanman (14), and many others have served to underscore the importance of congenital abnormalities that predispose to infection and premature death. In a report by Butler and Lanman (14) from the Children's Hospital in Boston, 54 per cent of infants and 79 per cent of children dying of pyelonephritis had anatomic malformation of the urinary tract. Further, the death rate from pyelonephritis with or without congenital abnormalities was higher in infancy than childhood, and pyelonephritis was more common as a cause of death from uremia than other forms of Bright's disease.

The pathology of pyelitis of infancy and childhood was clearly defined by Chown (15) from the Johns Hopkins Clinic of Pediatrics and the Department of Pathology in 1927 and by Wilson and Schloss from the Children's Hospital Clinic (16) in Boston. From that time the term pyelonephritis rather than pyelitis has been adopted.

It was in 1933 that Longcope and Winkenwerder (17) from this clinic reported on the clinical features of the contracted kidney due to pyelonephritis and stimulated new interest in the clinical course of the disease. They opened the discussion of their paper with this quotation, "If one has an opportunity to observe many cases of chronic Bright's disease, he will occasionally be surprised to discover that a patient, dying in uremia as a result of what was supposed to be chronic nephritis of the usual type has, in reality, at autopsy a

bilateral nephritis with shrunken kidneys and an irregular dilated pelvis. Or, if one has an opportunity to watch many children through adolescence to middle life, he may remember the rare instance of a child with persistent pyelitis who died when a young adult in uremia."

At that time there was little to be found concerning this particular form of pyelonephritis in textbooks, or indeed in the English literature as a whole. This paper struck fire and stimulated many to review their experience, first to re-examine whether or not pyelonephritis in infancy and childhood was a benign disease. It was soon discovered that in many instances pyelonephritis left its mark in the form of a latent or progressive infection, (Wharton, Gray and Guild (18)), and that a not inconsiderable number of children who failed to recover completely or who had signs of residual disease developed signs of renal insufficiency, hypertension and vascular disease. It came as a surprise to many that pyelonephritis was more commonly the cause of uremia than any other form of Bright's disease. So, a disease that starts in infancy and childhood and which may appear benign, may progress or show signs of periodic episodes of exacerbation and lead to premature death from uremia.

It is evident that all cases of pyelonephritis of infancy and childhood should be studied carefully and treated actively. A search should be made for congenital abnormalities that may be corrected and, what is most important, all of them should be followed in an attempt to prevent recurrences and to treat them promptly if they occur.

PYELONEPHRITIS OF PREGNANCY AND THE PUERPERAL STATE

That pyelonephritis is one of the common complications of pregnancy is common knowledge. It occurs as an acute disease during the course of gestation without any preceding history or signs of renal tract infection. Pregnancy may be responsible for an exacerbation of a chronic or recurrent pyelonephritis, and there may be accompanying signs of vascular or renal disease indicating a toxemia of pregnancy. Pyelonephritis is present in about 2 per cent of pregnancies and is predominantly unilateral and rightsided.

Infections of the kidney in the post partum period

If pregnant patients escape infection of the urinary tract during pregnancy, some may develop it in the post partum period (19). It has been stated by Randall and Murray (19) that about 15 per cent of patients are unable to void urine spontaneously after delivery. The factors contributing to this state are prolonged anesthesia or prolonged labor, spinal anesthesia, pelvic contracture with operative delivery, especially episiotomy, and delivery by forceps. Inability to void is much more frequent in primiparas who have had operative delivery. An attempt is made in these patients to prevent overdistention of the bladder and residual urinary retention after emptying the bladder. Since as

many as 45 to 50 per cent of these women develop an infection or infected urine, every attempt should be made to prevent it, and when it occurs to treat it promptly.

Pyelitis and toxemias of pregnancy

It was the late Dr. Jack Peters and his associates who directed attention to the importance of pyelonephritis as a precursor or associate of toxemias of pregnancy. That is to say, pregnancy can contribute a peculiar coloration to renal and vascular disorders when pyelonephritis, acute, healing or healed, is present. A relatively benign condition may advance to a malignant state and cause the frequency of renal and vascular disease in pregnant women to exceed that in non-pregnant women of comparable age. Moreover, there are reasons for believing that pyelonephritis of pregnancy may leave its mark and reduce the number of functioning renal units. It may be the initial infection and the starting point for a chronic active infection. It is evident that this form of Bright's disease should be recognized as an important associated feature of toxemia of pregnancy.

PYELONEPHRITIS OF THE ELDERLY AND IN CORD BLADDERS

It is common knowledge that obstructions of the lower urinary tract which cause stasis of urine, or diseases of the central nervous system or spinal cord that interfere with the emptying of the bladder, are often associated with pyelonephritis. This disease is especially common when it has been necessary to retain a catheter to empty the bladder. In recent years, we have been impressed by the high incidence of pyelonephritis, acute and healed, in patients with poliomyelitis or with traumatic paraplegia. In many of these patients, renal calculi are present which aggravate the infections. Renal biopsies by Dr. Relman and his associates in our clinic have demonstrated conclusively the high incidence of kidney disease in patients with poliomyelitis who have had to have inlying catheters to empty their bladders. These studies indicate that infections of the bladder are followed by infections of the kidney in a very high percentage of patients, regardless of the pathway of infection.

In all elderly people, then, with signs of pyelonephritis, the question of lower urinary tract obstruction should be explored, and in patients with cord bladders infection is one of the limiting factors in recovery.

ACUTE UNILATERAL PYELONEPHRITIS

It is customary to consider acute pyelonephritis of hematogenous origin a bilateral rather than a unilateral disease. However, a critical examination of the subject shows quite conclusively that unilateral pyelonephritis without demonstrable obstruction to the free flow of urine or other abnormalities on the affected side is not too infrequent.

The best studies of acute unilateral pyelonephritis have been made by surgeons who have studied such patients and removed kidneys during the acute stage and by experimental pathologists who have produced the disease experimentally and followed its course. These studies date from the beginning of this century. Those recorded by Brewer (20), Mallory, Crane et al (21) are most informative. Mallory and his colleagues have been able to reproduce all stages of the disease by causing partial obstruction of the ureter and a hematogenous infection. They have shown that the kidney has remarkable healing powers when no obstruction is present and rapid healing powers when the obstruction is removed. From these studies, we have gained important leads concerning the pathogenesis of pyelonephritis.

Within recent years, the healed or healing type of unilateral pyelonephritis has attracted wide attention because it is associated with hypertension in some cases and because removal of one kidney may be followed by reduction of blood pressure.

There seems to be no doubt that pyelonephritis may be unilateral or at least predominantly unilateral and that it may be recognized in its acute stage in children (22), in pregnancy and in older people.

Like bilateral disease, it may cause acute, rapidly progressive infections. It may heal, it may become chronically active and it may become associated with hypertension. The importance in recognizing it lies in its prevention when possible and in its treatment.

In the experimental studies of Mallory and Crane, "Extensive pyelonephritis was never found in the unobstructed kidney."

I turn now to some of the important anatomical lesions and complications associated with pyelonephritis—intrarenal, extrarenal, and systemic.

INTRARENAL LESIONS

Thrombophlebitis of renal vein

One of the pathologic features of some cases of acute pyelonephritis is septic thrombophlebitis of the renal veins. The presence of such a thrombus may lead to bacteremia and embolism to the lungs. The bacteremia from this site may give rise to foci of infection in other parts of the body. The presence of recurrent chills, fever and bacteremia in unilateral or bilateral pyelonephritis without a previous operative procedure should lead one to suspect this complication. It may aid in the decision of whether or not a nephrectomy should be performed.

Hematuria

In chronic pyelonephritis, gross hematuria is not usually a conspicuous feature. However, Braasch (23) directed attention to secondary renal hematuria

in 1938, and pyelonephritis as a cause of essential hematuria is recognized. Braasch reported an incidence of 12 per cent in 526 cases over a seven year period. It was usually accompanied by other signs of infection, but occasionally with little or no evidence of accompanying infection on examination except on bacteriologic examination of the urine and on proper therapy.

Hematuria occurring with acute infection of the urinary tract usually has its origin in the bladder. In pyelonephritis the bleeding arises in the kidney or ureter. It occurs later, i.e., after the disease has been present 10 or 20 years. Periodic and irregular profuse hematuria is due to granulomatous areas in the mucosa of the renal pelvis or ureter.

Renal hematuria in pyelonephritis is usually unilateral, rarely bilateral. Renal function may be normal, and the urographic deformity is absent about as often as it is present.

Secondary renal lithiasis

While it is generally recognized that renal stones are commonly followed by infection, it is to be remembered that lithiasis secondary to infection in bilateral pyelonephritis occurs in about 5 to 6 per cent of cases (Braasch), and in about one-third of the cases the stones are bilateral. Bilateral stones are usually multiple, unilateral stones are more often single. One point of interest is that when chronic bilateral pyelonephritis exists with a stone in one kidney, the infection is usually primary, because infection occurring secondary to stone is seldom transmitted to the other kidney.

The clinical features of these cases differ somewhat from those of primary lithiasis. They cause very little trouble aside from serving as a factor in continuing infection. Renal pain is of secondary importance, dysuria and polyuria are more important. Passing stones and x-ray evidence of stones are frequent. The evidence of destruction of kidney tissue is not aggravated.

There are usually multiple small shadows scattered over the kidney or confined to one pole, generally 2 to 4 mm. in diameter and often irregularly rounded. Often they are localized to the apices of the calyces or beyond. They may suggest calcium deposits in the tubules rather than actual stone formation.

Stone formation secondary to infection has been a topic of intensive investigation because of the biochemical factors involved. It has been observed most often in the infections associated with an alkaline urine. The commonly accepted view is that certain microörganisms, notably *B. Proteus* and many strains of staphylococci, are capable of splitting urea into ammonia, which produces an alkaline urine, and the presence of calcium phosphate in the urine, in the presence of an excessive amount of alkali, leads to precipitation of the salts with stone formation. This is aggravated if an attempt is made to acidify the urine with ammonium chloride or if there is prolonged rest in bed or an increase in calcium intake in the form of milk. In any event, secondary lithiasis

is an important complication of many forms of pyelonephritis. Attempts should be made to prevent it by recognizing the disease early and attempting to eradicate it.

EXTRARENAL LESIONS

Spontaneous perirenal hematoma

An infrequent feature of unilateral pyelonephritis is a spontaneous perirenal hematoma (24). The cause of the bleeding is an erosion of a blood vessel of the cortex of the kidney, with bleeding into the perirenal tissues. In my experience this has occurred in patients with renal infection, associated with hydronephrosis and nephrolithiasis. The story is that of recurrent attacks of unilateral pyelonephritis associated with renal colic and the sudden onset of a severe attack of pain in the flank and abdomen, soon followed by collapse, the signs of internal bleeding, and the development of a mass in the flank with elevation of the diaphragm on that side. Anemia, leukocytosis and slight icterus (hematin icterus) may follow. In these cases there are signs of urinary tract infection, and hematuria may be present as well. The treatment is removal of the hematoma and nephrectomy.

OTHER INFECTIONS

Infection of the perirenal fatty tissues is a not infrequent associated feature of acute and chronic pyelonephritis. It may be unilateral or bilateral, but more often it is on one side. It is associated with calculous disease of the kidney or with pyelonephritis without stones. As a rule, renal calculi are treated early and removed, and today pyelonephritis is recognized early in its course and treated promptly, but one of the features of these infections of the kidney when they are uncontrolled and chronic is the overgrowth of fatty tissue and induration of the connective tissues about the kidney. In extreme cases the kidney substance is atrophied and completely replaced by fat. These indurated areas may be present as masses in the flank and may be mistaken for tumors of the kidney.

In all patients with pyelonephritis, the perirenal tissues should be remembered as areas of infection.

Other infrequent complications of acute pyelonephritis with perinephritis are fistulae that open into the bronchus (25), or the spread of the infection from the perirenal space into the pleura and lung. There may be direct spread through the costolumbar hiatus, by means of which the subpleural fat communicates with the perirenal fatty tissue.

My point in mentioning these extrarenal infections is to stress the fact that infection may spread beyond the capsule of the kidney and produce signs and symptoms as well as complications that may be exceedingly difficult to deal with. In summary, the extrarenal lesions are perirenal hemorrhage with hema-

toma, perinephritis with abscess, perinephritis with fibrosis and fatty replacement and extension of infection from perirenal space to the pleura.

GENERAL SYSTEMIC REACTIONS

Amyloidosis

Between 5 and 10 per cent of patients with chronic, non-tuberculous pyelonephritis and chronic infections of the urinary tract develop amyloidosis. The mechanism for this response in the organs continues to remain obscure.

Calcinosis and secondary hyperparathyroidism

The presence of chronic pyelonephritis with renal insufficiency of several years' duration may lead to the development of the signs of calcinosis with extensive calcification of the blood vessels and deposits of calcium in the soft tissues, especially about the joints. The sequence of events in these cases is somewhat as follows. Following a long-standing pyelonephritis (one to nine years) with renal insufficiency, there is a retention of phosphates, enlargement of the parathyroid glands, demineralization of the skeleton due to the hyperactivity of the parathyroid glands, chronic acidosis, chronic loss of calcium phosphate in the stools, and finally the precipitation of calcium phosphate and perhaps carbonate in the tissues of the skin and internal organs.

Jaundice associated with pyelonephritis

The association of jaundice and pyelonephritis has been observed and made the subject of comment by several observers. Görter and Lignac (26) observed jaundice in pyelonephritis of children, and it has been noted also in patients associated with pyelonephritis of pregnancy. Felty and I (27) recorded the presence of jaundice in patients with *E. coli* sepsis following urinary tract infection who had been observed in this clinic. Since then, I have observed patients with pyelonephritis and jaundice associated with pregnancy, with renal calculi, and with multiple septic infarcts of the lung, or metastatic bronchopneumonia.

In infants and children with pyelonephritis, and in patients with renal stones, pyelonephritis, and metastatic bronchopneumonia and jaundice, the prognosis has been grave. In those with pyelonephritis of pregnancy, the presence of jaundice has not necessarily increased the gravity of the infection. In any patient, however, who has pyelonephritis and who later develops jaundice, one should consider the presence of bacteremia or associated lesions such as bronchopneumonia, pulmonary infarction, or associated infectious hepatitis or cholangitis.

Bacteremia

Bacteremia in urinary tract infections and in pyelonephritis is commonly observed following instrumentation, operations or catheterizations, or any

traumatic action of the urinary tract. When it arises spontaneously, i.e., without previous trauma, one should consider either thrombophlebitis of the intralobular veins or a necrotic papillitis. Bacteremia is an index of severity of the local lesion and of the inability of the normal clearing mechanism to clear the blood promptly. It calls for intensive active treatment.

Bacteremia may be followed by septic metastases in the endocardium, the lungs, and other organs.

SUMMARY

In short, then, acute pyelonephritis may be acute in its course and gradually subside or it may cause rapid deterioration and death from uremia or sepsis. The lesion may heal and renal function return to normal and the urine remain clear. There may remain only a few focal scars. Only too often, however, the acute infection subsides but a chronic active infection persists and progresses, often with acute exacerbations. In others, after an indeterminate period of time, the kidney lesion heals with a reduced renal function. In these cases, the disease may remain latent for long periods of time until hypertension or nitrogen retention or toxemia of pregnancy direct attention to the kidneys.

The acute process may be unilateral or bilateral and may be associated with many intra and extra renal features.

CHRONIC PYELONEPHRITIS

It was in November 1933 that the classic paper of Longcope and Winkenwerder (17) appeared describing and focusing attention on the clinical features of the contracted kidney of pyelonephritis. (This outstanding contribution stimulated others to review their experience and led to a better understanding of the problem.) From Longcope's description and later from the studies of Weiss and Parker (28), it became clear that, while the course of chronic pyelonephritis varies in certain particulars depending upon such factors as activity of infection of the kidney, the degree and duration of hypertension, the severity of the anemia and the complications that may arise, there are certain features that occur with a degree of regularity and uniformity. They are the long insidious course (one to ten years or longer), the frequency of the disease in women under the age of 40, the gradual loss of weight and dry skin, the peculiar features of the urine, i.e., minimal traces of albumin with lack of casts and erythrocytes and variable degrees of pyuria, the absence of signs and symptoms of cystitis with abnormalities of the pyelogram, the progressive anemia, the renal insufficiency, and the sudden termination with or without hypertension in uremia.

Weiss and Parker (28), in discussing and describing the cases of chronic and healed pyelonephritis associated with hypertension, directed attention to the following features. 1) The hypertension of pyelonephritis is often severe and may be present with normal, adequate or poor function of the kidney.

2) It is frequently accompanied by nervous symptoms including hypertensive encephalopathy, neuroretinitis, high cerebrospinal pressure and toxemia of pregnancy. 3) Cardiac asthma and left ventricular failure may be present. 4) Organic diseases of the cerebral and coronary arteries are rare in contrast to those associated with chronic hypertension or to "malignant" nephrosclerosis of other causes. 5) The hypertension of pyelonephritis can be independent of the activity of the renal infection. *It often advances when the disease is in the healed stage.*

Pyelonephritis lenta

In order to stress the fact that pyelonephritis is often latent and insidious in its course until hypertension and renal failure appear, Saphir and Taylor (29) have described what they choose to call *pyelonephritis lenta*. This is a disease of insidious onset with a presenting sign of hypertension, in patients under 50 years of age, with anemia, albuminuria, and other inconstant urinary findings such as cylindruria and an increase in leukocytes. The kidneys are smaller than normal with shallow, yellowish pink, contracted scars and scars of the pelves. The heart is uniformly enlarged. There are necrotizing and inflammatory lesions in the kidney. Uremia is precipitated by an acute exacerbation of the pyelonephritis in 50 per cent of cases.

HYPERTENSION

One of the curious features of pyelonephritis, either unilateral or bilateral, is the irregular association of the kidney disease with vascular disease or hypertension. Everyone who has studied the relationship between pyelonephritis and hypertension has reached the same conclusions; namely, that some patients with bilateral pyelonephritis die in uremia with normal blood pressures, some develop hypertension before signs of renal insufficiency, and others develop it after it occurs (28). In the cases described by Longcope, hypertension was present in half the cases and in 9 of the fatal cases, 6 had hypertension during life and only 5 showed arteriosclerosis, which was never profound or extensive. Weiss and Parker (28), on the other hand, noted a relation between the severity and diffuseness of the vascular lesions and the arterial hypertension, because the patients with severe hypertension had advanced vascular disease with hyperplastic arteriosclerosis, productive endarteritis and necrotizing arteriolitis. It was their opinion that the hypertension was renal in origin.

In the study of the relation of hypertension to vascular disease or of vascular disease to hypertension, or renal disease to localized disease of the blood vessels of the kidney and hypertension, one must take into account the genetic factors involved in the pathogenesis of vascular disease and of hypertension. Genetic factors are exceedingly important in the investigation of both hypertension and vascular disease, and the outstanding long-range studies of Thomas

(30), Pickering (31, 32), and others have been most important in promoting a better understanding of the total problem.

How renal disease, such as pyelonephritis with occlusion of the blood vessels and other kidney disorders that reduce the blood supply to the kidneys, may accelerate or intensify hypertension, or on occasion bring it into being, is an unsettled problem that requires continuing or long continued investigation.

Vascular disease

In the patients with chronic pyelonephritis who were studied by Longcope, the tissues being reviewed by Rich, the vascular disease was neither profound nor extensive. Of the 9 fatal cases, 6 had elevated blood pressure during life, 5 showed arteriosclerosis, and in 2 it was minimal in degree. In 3 it was combined with chronic glomerulonephritis. Weiss and Parker (33) commented on the fact when vascular changes occur in pyelonephritis, particularly during the chronic and healed stages, they are restricted mainly to the kidneys. Further, the vascular changes can be correlated with the hypertension more than with the size and functional capacity of the kidneys. It was the contention of some that the vascular lesions result from the inflammatory renal process and the intravascular pressure, and that these lesions in turn lead to renal ischemia and hypertension.

There are two reasons for recognizing the hypertension associated with pyelonephritis. First, when it is associated with unilateral disease, it may be possible in at least 20 per cent of cases to relieve the hypertension by nephrectomy, and perhaps in some cases prevent the accelerated phase of hypertension.

Second, pyelonephritis is the commonest associated renal cause of hypertension and should always be suspected in any patient under 40 years of age with high blood pressure. While hypertension is observed in healed pyelonephritis and without signs of active infection, the kidney disease should be recognized, because such patients may have an acceleration of their hypertension with an increase in the levels of blood pressure and deteriorate rapidly if they get a reinfection, or the hypertension may accelerate due to genetic factors that become operative before 50 years of age. In such patients, the blood pressure can often be lowered with hypotensive drugs whether they have entered the accelerated phase or not, just as the accelerated or malignant phase may be reversed to a benign phase by any method that lowers blood pressure such as sympathectomy, adrenalectomy or hypotensive drugs.

Certainly there are methods available at present for prolonging life, alleviating symptoms and studying the effect of lowering blood pressure or the course of the disease so that we may learn more about the multiple factors that contribute to the entire picture.

Unilateral renal disease with hypertension

Pyelonephritis, acute, healing or healed, may involve only one kidney and go unrecognized until hypertension appears. Since the classical studies of Goldblatt in 1948 (34), there has been accumulating a large body of evidence to the effect that a certain number of people with unilateral kidney disease, usually pyelonephritis, develop hypertension and in a certain number, i.e., 20 per cent, the removal of the involved kidney is followed by relief of the hypertension and return of blood pressure to normal. This subject has been reviewed over and over again, and in an exhaustive manner by Smith (35).

One of the more important studies of unilateral kidney disease and its relation to hypertension has been made by Perera and Hailey (36) in their analysis of the clinical characteristics of the hypertension associated with unilateral kidney disease. They approached the problem by comparing a group of 20 patients who were "cured" of their hypertension by unilateral nephrectomy and compared them with a group who were unimproved. They pointed out that the patients with unilateral kidney disease who were improved by nephrectomy usually had unilateral pyelonephritis, and that the hypertension was of the acute, severe, rapidly progressive type and it was of relatively short duration, i.e., less than two years. They suggested that when hypertension appears for the first time in people over 50 years and pyelonephritis is present and unilateral, these people are most likely to benefit from nephrectomy.

We urgently need additional information about the relation of unilateral kidney disease to hypertension. Also, we need to know what role the genetic factors play in bringing the hypertension into being. If the observations of Perera and Hailey (36) can be extended and confirmed elsewhere, then valuable information concerning the indications for unilateral nephrectomy as a means of relieving hypertension will be developed.

Weiss and Parker made the important observation that in unilateral pyelonephritis, and particularly in cases without severe hypertension, the vascular lesions are confined to the affected side. Further unilateral pyelonephritis with advanced vascular changes, regardless of the size of the kidney, may or may not be associated with hypertension. This tends to point up the fact that there are many missing links in this chain of unilateral kidney disease, vascular disease and hypertension. In 20 cases reported by Weiss and Parker, 8 patients were under 50 years of age. Only 3 of these 8 patients in whom the blood pressure was recorded had diastolic hypertension, and only 1 died in uremia, whereas 7 of 12 patients over 50 years of age had diastolic hypertension and 3 died of uremia, 2 with hypertension and 1 without it. Uremia was precipitated in this patient by acute pyelonephritis.

TREATMENT

It was Pasteur who first directed attention to the fact that urine was an excellent culture media for bacteria. Moreover, he was the first to direct attention to the highly important observation that bacterial antagonism occurred when two organisms were grown in urine. That is to say, anthrax bacilli were often killed by streptococci. This was the observation that finally resulted in the development of antibiotics.

The treatment of acute and chronic pyelonephritis has been the subject of intense study for many years, and, while some progress has been made in the control of many of these infections, there are many unsolved problems. They remain as a challenge to the imagination of all physicians regardless of their specialties. We need to know more about the pathogenesis of these infections and the various mechanical, anatomical and biological factors that promote reinfection, chronicity and resistance to treatment. If we were able to advance knowledge and could learn how to prevent and control these infections, we would prevent much disability and physical impairment. We would prevent many premature deaths from infection, from hypertension and its complications, and from uremia. Each patient presents a specific problem and should be treated after a careful survey of the status of his urinary tract infection.

The problems of treatment have become highly complicated and technical, and the literature on the subject is voluminous. Excellent reviews have been made during the past few years by Kass (4), Birchall and Alexander (37), Beeson (38), Rhoads, Billings and O'Conor (39), and others.

Any plan of treatment of urinary tract infections should include a definite course of action based upon sound information and individual judgment, because no two patients present the same problems and no two patients are alike. Any plan should include a program of prevention. The disease should be recognized promptly, the causative organism or organisms identified, the presence or absence of complicating factors recognized, and the antiinfective agent or agents selected on the basis of appropriate tests and studies.

At the risk of oversimplification, I propose to summarize the present status of treatment, based upon my own experience and that of others as it has been recorded.

GENERAL CONCLUSIONS

Acute, uncomplicated urinary tract infections of short duration, due to a single strain of microörganisms susceptible to antibiotics or antiinfective agents, can be cured in 90 per cent of cases. Single species of bacteria are found in the urine in 80 to 90 per cent of patients with acute, uncomplicated pyelonephritis.

Chronic, complicated urinary tract infections of long duration, due to single or multiple strains of bacteria which are sensitive to antiinfective agents, can be eliminated temporarily in 70 per cent of cases. Infections complicated by structural abnormalities of the urinary tract show single species of organism in only 20 to 30 per cent of cases, and mixed infections in the remainder.

Between these two groups, there are many variations due to a variety of factors such as reinfection, the appearance of drug-resistant bacteria and structural abnormalities that cannot be corrected.

Thus, it has been found that reinfection with drug-resistant strains of bacteria, often of the same species, is exceedingly common, so that the permanent control rate with sterilization of the urine in chronic, complicated infections may be no greater than 10 per cent.

Reinfection of the urinary tract plays a large role in the lack of permanent control of infection and is often introduced by catheters or similar instruments. Cross infections on wards that are presumed to be passed through the medium of inlying catheters or other instruments are important. Reinfection is most common in patients with chronic, complicated urinary tract infections, most often in the presence of some obstructive lesions.

Prophylactic therapy when used with catheterization may create new problems by reducing pyuria and encouraging the appearance of drug-resistant strains.

The attack should be made early, and attempts should be made to select the most potent antiinfective agent available and to treat the patient intensively and with combinations of drugs which are most likely to have an optimum effect.

Penicillin is most useful in the management of staphylococcic and enterococcic infections and in some *Proteus bacillus* infections due to *P. mirabilis*.

Streptomycin or combinations of streptomycin and dihydrostreptomycin combined with alkali and given for five to seven days in full therapeutic doses, 1 gm. a day, and keeping the urine at a pH of 8, is most useful in Gram-negative bacillary infections and when combined with other agents, such as penicillin in the management of enterococcic and staphylococcic infections.

Polymyxin and neomycin are usually too toxic for use except in exceptional cases of a serious nature where the organisms are resistant to other antibiotics.

Chlortetracycline, oxytetracycline and tetracycline all have a place and are potent agents. They clear susceptible organisms from the urinary tract. Sensitivities to each of these agents should be carried out whenever one is faced with a difficult problem, because while the clinical differences are not great between the three, in some cases they are important.

SUMMARY

To sum up, acute and chronic pyelonephritis is a common infectious process involving one or both kidneys, usually caused by the Gram-negative bacillary

group of microörganisms. The acute disease is seen most often in infants and children, in women during the childbearing period, and in elderly men or women with lower urinary tract infections usually associated with obstruction. It is especially common in patients with diabetes and acute attacks may be precipitated by catheterization, instrumentation, or operations on the urinary tract. The inflammatory process involves primarily the interstitial tissues of the pyramids and the cortex. The acute phase of pyelonephritis may be rapidly progressive and cause death from sepsis or renal insufficiency or both, or it may be followed by complete healing with focal scar formation in the kidney and normal renal function. Not infrequently, the acute process subsides but an active infection persists and a chronic active infection supervenes This phase may be latent or asymptomatic until advanced renal insufficiency develops. A number of patients with chronic active infection have acute exacerbations of their infections during pregnancy or the postpartum period without any other special precipitating factor.

In some cases the acute phase of pyelonephritis is not evident, so that a chronic active disease proceeds slowly and progressively with a continuing destruction of functioning nephrons, which are gradually replaced by scar tissue and by changes in the blood vessels that ultimately leads to renal ischemia. Renal failure and hypertension may appear together or separately. It is not uncommon for renal insufficiency and hypertension to appear after complete healing of the active process has occurred. The triad of chronic infection, hypertension with vascular phenomena or uremia may occur in any combination and make up the clinical picture.

Chronic pyelonephritis with uremia is the commonest cause of death from renal disease. When the disease is unilateral and is associated with hypertension, the high blood pressure may be relieved by unilateral nephrectomy. This occurs in about 20 per cent of cases of hypertension associated with unilateral kidney disease. Nephrectomy is indicated in people with unilateral pyelonephritis who have diastolic hypertension of short duration, i.e., less than two years.

Chronic and healed pyelonephritis is often associated with hypertension. In Longcope's carefully studied cases, hypertension was present in 50 per cent. The hypertension may be present without signs of an active renal infection, and it is unrelated to renal function. Some believe that it is related to the renal ischemia that follows the associated renal vascular disease. This is a problem requiring further study, especially to determine the genetic or hormonal factors in hypertension and in vascular disease.

Hypertension of bilateral pyelonephritis can be lowered and relieved by sympathectomy or by hypotensive drugs.

Antiinfective therapy and the surgical removal of obstructive lesions are extremely important in the control of infections. We urgently need new information of a basic nature concerning the pathogenesis of renal tract infec-

tions, and we need more basic information about the biological behavior of bacteria in the kidney, how they arrive there, why they are so difficult to eliminate, and why reinfection is so common.

Of all chronic bacterial diseases, urinary tract infections are among the most difficult, the most perplexing and the most disturbing, yet their study may be the most rewarding. We have reason to believe that continued efforts to study this disease in its dramatic and undramatic episodes will bring very worthwhile results. The goal should be to prevent infections and to eliminate infective agents when they occur. In this way, much suffering and many premature deaths will be prevented.

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INAPPARENT DIABETES MELLITUS AS A CAUSE OF RENAL INSUFFICIENCY DUE TO KIMMELSTIEL-WILSON LESIONS

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INTRODUCTION

Kidney lesions associated with diabetes mellitus[2] were described in 1936 by Kimmelstiel and Wilson (1). The lesion which many regard as specific for diabetes has the appearance of an intercapillary hyaline ball. On the basis of seventeen subsequent cases reported in the literature in which these nodular lesions have been found in "non-diabetics", the specificity of this lesion for diabetes has been questioned (2–7). Kimmelstiel himself, in his last evaluation of the problem states that "there can be no doubt that the nodular type is occasionally observed in cases in which diabetes can reasonably safely be excluded" (8). He does not document this statement and, indeed, in his summary he states that the nodular lesions can be regarded as "almost specific" for diabetes. Robbins, Rogers and Wollenman however, are convinced that these nodular lesions are found only in diabetics (9).

It is the purpose of the present report to describe two cases which support the view that in patients in whom Kimmelstiel-Wilson lesions are found, a complete study of the past history, the availability of adequate laboratory data and a careful study at autopsy would provide evidence of the presence, at some time in the patient's life, of diabetes mellitus. It is noteworthy that the renal lesion in these patients, whose diabetes was never detected on the basis of blood and urine sugar content, was so extensive as to be the major cause of death.

Case 1. J. H. H. History No. 331258. B.M., a 65 year old white married female was admitted to the medical service September 2, 1944, with a complaint of weakness and diarrhea of one week's duration. The patient died nine weeks later. No one in the patient's family was known to have had hypertension, kidney disease or diabetes. The patient had had an episode of jaundice fifteen years previously. No details regarding this illness were available. Two years previous to admission she began having exertional dyspnea. The patient stated she was in good health, however, until four months before admission, when she developed massive dependent edema extending up to her umbilicus. At this time she also had numbness and

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[2] The term diabetes mellitus is here taken to mean that disorder of carbohydrate metabolism characterized by a decreased ability to utilize glucose which exists in the absence of detectable hyperactivity of the thyroid, pituitary or adrenal glands, in an individual who up to the time of testing has been consuming ample amounts of carbohydrate.

tingling of her hands and feet, symptoms which had appeared in a mild form two years previously. Diarrhea and two episodes of vomiting occurred during the first week of illness. There were no urinary abnormalities save for mild nocturia, which began at this time. A private physician gave the patient digitalis with resultant disappearance of much of the edema. The patient noted extreme weakness coming on two months later, during which period she is said to have lost weight. One week before admission the patient began having four to six watery bowel movements a day.

At the time of admission the patient was noted to be emaciated and to have "mild" edema of the legs. The blood pressure was recorded as 225/85. There was definite puffiness about the eyes. There were "tiny punctate retinal hemorrhages" noted in addition to arteriosclerotic vascular changes. The heart was enlarged to the left. There were rales at both lung bases. The deep tendon reflexes were absent. Vibratory sense was absent below the waist. Position sense was impaired in the toes.

The patient's course in the hospital was characterized by intermittent diarrhea and mild constipation. Five hundred cc. of fluid was removed from each pleural cavity. Coincident with a progressively rising serum non-protein nitrogen, consciousness became clouded. Pruritis, stupor, and hallucinations followed. Death occurred November 5, 1944.

The serum non-protein nitrogen was 72 mgm. per cent at the time of admission. Following a decrease to 54 mgm. per cent there was a progressive rise to 113 mgm. per cent. This last value was obtained October 27, 1944. The hemoglobin was 9.5 gm. per cent on admission. This fell to 7.1 gm. per cent October 19, 1944. The serum carbon dioxide, chloride, cholesterol, calcium, phosphorus and total bilirubin were within normal limits on admission. The total serum protein concentration was 4.81 gm. per cent with 2.94 gm. per cent as albumin. A blood sugar of 153 mgm. per cent on admission was said to have been non-fasting. A repeat fasting blood sugar four days later was 123 mgm. per cent. Bromsulphalein retention was 5 per cent in thirty minutes. The basal metabolic rate was minus 3. On October 27, 1944 the serum calcium was 8.4 mgm. per cent, phosphorus 7.5 mgm. per cent, carbon dioxide combining power was 15.3 mEq. per liter and chloride 113.5 mEq. per liter. Thirteen urinalyses were performed. No sugar was ever detected. Urinary protein varied from three to four plus. Occasional red and white cells and many granular and hyaline casts were seen in the sediment. The specific gravity of the urine varied from 1.010 to 1.018. Stool specimens obtained were either guaiac negative or one plus positive for blood. The patient's weight was about 80 pounds throughout her hospital course. Previous weights were not known. Two upper gastrointestinal x-ray series did not reveal lesions. A barium enema was not satisfactory. At the time of death the patient was thought to have had: chronic glomerulonephritis, hypertensive and arteriosclerotic cardiovascular disease and uremia with (?) uremic or tuberculous enteritis or (?) gastrointestinal malignancy.

At autopsy (No. 19200) the body weighed 39.5 Kg. and measured 140 cm. in length. In addition to the findings of generalized arteriosclerosis, a slightly enlarged heart and slight pulmonary edema, there was hyalinization of many of the islets of Langerhans (Fig. 1) and an advanced form of nodular lesions of Kimmelstiel and Wilson in the kidneys (Fig. 2). The kidney did not take stains for amyloid. The liver, adrenals, thyroid and pituitary were normal. In addition, there was a mucus-forming adenocarcinoma of the cecum measuring 5.0 x 4.0 x 2.0 cm. No metastases were found. The eyes were not obtained for examination.

In summary, this 65 year old white female with signs of neuropathy and

"tiny retinal hemorrhages" had no evidence of diabetes as judged by fasting blood sugar and urine sugar determinations. She died of renal insufficiency and was found to have had typical lesions of nodular intercapillary glomerulosclerosis in addition to hyalinization of the islets of Langerhans. There was slight renal arteriolosclerosis and generalized arteriosclerosis. No history of illness or symptoms referable to diabetes was obtained from this patient save for paresthesias, which may have been due to her anemia, which began two years and became more severe four months prior to admission.

Case 2. J. H. H. History No. 697526. E.C., a 63 year old white male carpenter was admitted to the Johns Hopkins Hospital for the first time, February 23, 1955, because of shortness of breath of five months duration. The patient was said to have had right flank pain in 1935, following which he passed "sand" in his urine. The patient was found to have choroiditis of the right eye in 1948. In 1949, he was admitted to the Franklin Square Hospital because of non-radiating pain in the right leg of three to four months duration. Blood pressure was 142/72; eyegrounds were normal. The impression on physical examination was neuritis, ? etiology. An x-ray of the lumbar spine revealed narrowing of the fifth intervertebral space and changes of hypertrophic arthritis. The hemoglobin was 16.0 gm. per cent, white blood cell count 6,700, serum non-protein nitrogen 43 mgm. per cent, fasting blood sugar 87 mgm. per cent. A urinalysis revealed a slight trace of albumin, O-sugar, specific gravity 1.016 and an occasional white blood cell in the sediment. The patient was discharged and remained entirely asymptomatic until 1952–53 when he began having severe polydypsia and polyuria amounting to as much as six to eight liters per day. Despite these symptoms the patient felt he was in good health until the Spring of 1954, when he began feeling weak, tired and had a decrease in his appetite, the latter resulting in a 10 pound weight loss over the next six months. In September, 1954, he consulted a physician who found his weight to be 128 pounds. Weights previous to this time were not known. The hemoglobin was 54 per cent of normal, red blood cell count 2.9 million and the blood urea nitrogen 70 mgm. per cent. The patient was admitted to the Sinai Hospital that same month where his blood pressure was found to be 190/90. The right fundus revealed a healed choroiditis. The heart was enlarged. There was no edema. On admission the blood urea nitrogen was 164 mgm. per cent, fasting blood sugar 63 mgm. per cent, serum phosphorus 6.0 mgm. per cent and carbon dioxide 13.1 mEq. per liter. The remainder of the laboratory examinations of the blood including total protein and albumin and globulin were normal. Urinalyses revealed a specific gravity which varied from 1.007 to 1.010, three plus albumin, no sugar, zero to four white blood cells per high power field and a few granular and hyaline casts. There was fifteen per cent excretion of phenolsulfonphthalein in two hours. Four blood transfusions brought his hematocrit to 47. Urine output during the twelve days in the hospital varied from 750 to 1850 cc. per day while on an unlimited fluid intake. The patient was discharged and followed by his private physician. In January, 1955, the phenolsulfonphthalein excretion was 35 per cent in two hours; in February the serum non-protein nitrogen reached a low of 47 mgm. per cent. His hematocrit was steady in the 40's until February, when it fell to 26. Shortness of breath became a prominent symptom and the patient was once again admitted to the hospital. The family history was negative for diabetes and kidney disease. The patient's father died of "gland trouble". His mother died of heart disease, and one brother had "Christian's Disease" with skin and bone lesions. The patient was admitted to the Johns Hopkins Hospital on February 23, August 10, October 25 and November 10, 1955. His course was characterized by mild congestive heart failure, anorexia, nausea, vomiting, anemia and progressive azotemia. The

blood pressure remained at mild hypertensive levels. The serum non-protein nitrogen rose to a height of 250 mgm. per cent three days before death. Four fasting blood sugars were performed during this nine month period. The results were: 92, 88, 117, 117 mgm. per cent. Albuminuria varied from two to four plus. The serum cholesterol on October 28 was 230 mgm. per cent. The patient died November 17, 1955 following a twelve hour episode during which he went into pulmonary edema, became severely hypotensive and was semi-comatose with muscular twitching.

At autopsy (No. 26108) there was two plus pitting edema of the ankles. The body weighed 114 pounds and measured 175 cm. in length. There was moderate left ventricular enlargement. The lungs were edematous. The kidneys showed the advanced lesions of nodular intercapillary glomerulosclerosis (Fig. 3) and slight arteriolosclerosis. The pituitary revealed diffuse scarring and a rather large area of fresh necrosis. The adrenals, thyroid and liver were normal. The pancreas was normal. The heart, pituitary and kidneys did not take stains for amyloid.

In summary, this 64 year old white male had a history of severe polydypsia and polyuria two to three years before the onset of symptoms relating to renal insufficiency which resulted in his death sixteen months later. At autopsy, advanced nodular Kimmelstiel-Wilson lesions were found in the kidneys. There was also extensive scarring and an area of fresh necrosis of the pituitary. The patient's weight loss over a two year period of observation was 25 pounds.

DISCUSSION

Two patients have been presented who were found to have severe nodular Kimmelstiel-Wilson lesions at autopsy. Despite the absence of hyperglycemia and glycosuria in these patients, a careful review of the clinical records in addition to the findings at autopsy make it very likely that these patients were diabetic, since one of them had widespread hyalinization of the islets of Langerhans, and the other had partial destruction of the pituitary which could have masked a diabetic state in addition to a past history of polydypsia and polyuria.

In reviewing the cases of nodular Kimmelstiel-Wilson lesions reported in "non-diabetics" (2–7) it is seen that evidence suggestive of diabetes may be found in most instances on examination of either the clinical history or autopsy report. No clinical data are available in seven of these cases (2–5). There was a "family history" of diabetes in two cases (2). Hyperglycemia "which may not have represented a fasting value" was found in one case (3), and glycosuria of minimal degree, with inadequate data to establish the diagnosis of diabetes, in two others (4, 5). Three cases were found to have hyalinization of the islets of Langerhans at autopsy (3, 7), and retinal "capillary aneurisms" were described in another (7). Aside from the three patients in whom hyalinization of the islets was found, there is no information regarding the state of the pancreas. In none of these patients is information available pertaining to the condition of

the pituitary and adrenals at autopsy or to the possibility of the patient having lost weight. It should be emphasized that the diagnosis of diabetes mellitus was not excluded in any of the above mentioned patients. Bell (6), however, mentions two cases with Kimmelstiel-Wilson lesions in which diabetes was said to have been "definitely excluded". No data are presented to support this statement. In addition, three "non-diabetics" who were found to have nodular Kimmelstiel-Wilson lesions at autopsy, on investigation into past hospital records, were proven definitely to have had diabetes (10).

Three unequivocal situations in man which may cause amelioration of the carbohydrate defect of diabetes mellitus are destruction of the anterior pituitary (11), destruction of the adrenals (12) and weight loss in a previously obese patient (13). Liver and thyroid disease may also profoundly influence carbohydrate metabolism (14). The effect of weight loss in an obese diabetic may be so great as not only to eliminate the need for insulin, but in addition to bring the glucose tolerance test to within normal limits. One such patient described by Newburgh (13) subsequently failed to develop glycosuria during an episode of lobar pneumonia. The primary obstacle in the discovery of mild carbohydrate defects is the common practice of performing a glucose tolerance test only if there is glycosuria, hyperglycemia or a history of diabetes.

Four cases further emphasize the impossibility of declaring a patient a non-diabetic without complete clinical histories and adequate laboratory studies including a glucose tolerance test. There have been three reports of known diabetics not receiving insulin, with nodular Kimmelstiel-Wilson lesions found at autopsy whose blood sugars had been normal before death. One of these patients (15) had an abnormal glucose tolerance test at a time when the fasting blood sugar was normal. The two other cases (16, 17) were found to have had normal blood sugars shortly before death; glucose tolerance tests were not performed at that time. An additional patient (18) with heart failure, albuminuria and a normal blood and negative urine sugar was found to have an abnormal glucose tolerance test which was performed solely because of the presence of birefractile fat droplets in the urine. This patient died of heart failure and was found to have nodular Kimmelstiel-Wilson lesions at autopsy.

It is clear that the Kimmelstiel-Wilson lesions complicating diabetes mellitus may occur in the presence of a carbohydrate defect so mild as to require a glucose tolerance test for its detection (18). The cases presented in this report make it very likely that Kimmelstiel-Wilson lesions may cause the death of patients without diabetes ever having been diagnosed on the basis of symptomatology, blood or urine sugar content.

SUMMARY AND CONCLUSIONS

Two patients are described who died from renal failure caused by the Kimmelstiel-Wilson type of glomerular damage known to be associated with di-

abetes mellitus. The blood and urine sugar values were within normal limits for the entire time they were medically observed. Despite this, when consideration is given to symptomatology and autopsy findings, these patients in all probability should be considered to have had diabetes mellitus, particularly since one of them had widespread hyalinization of the islets of Langerhans, and the other had partial destruction of the pituitary which could have masked a diabetic state. The cases are presented in support of the view that the nodular type of Kimmelstiel-Wilson lesion is specific for diabetes.

It is emphasized that a normal blood sugar and a negative urine sugar throughout the observed course of the patient's illness are not sufficient to dismiss diabetes mellitus as a possible cause of retinitis, peripheral neuropathy and chronic renal insufficiency.

ACKNOWLEDGMENT

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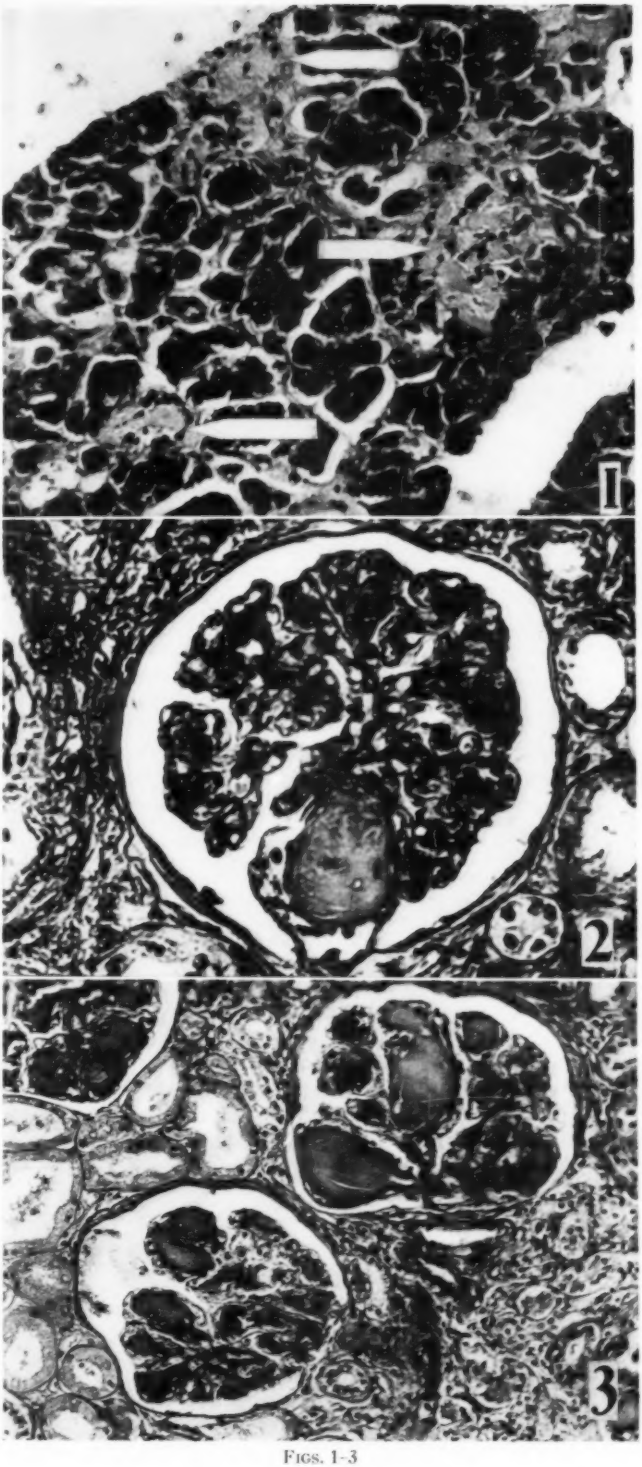
EXPLANATION OF FIGURES

FIG. 1. Case 1. Pancreas. Hyalinized islets of Langerhans. H. & E. ×200.
FIG. 2. Case 1. Kidney. Nodular Kimmelstiel-Wilson lesion. H. & E. ×350.
FIG. 3. Case 2. Kidney. Nodular Kimmelstiel-Wilson lesions. H. & E. ×110.



FIGS. 1-3

ABSTRACTS OF PAPERS PRESENTED BEFORE THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

December 10, 1956

A WETTING AGENT FOR BLOOD CLOT

MORRIS ROSENFELD

This paper was published in the October issue of the Bulletin of the Johns Hopkins Hospital.

PACEMAKER MECHANISM

STEPHEN W. KUFFLER

The main thesis of this discussion states that the pacemaker mechanisms in the heart represent a specialization of a wider cellular phenomenon. A common property of all cells which show "pacemaker activity" is autorhythmicity or spontaneous activity. It is pointed out how difficult it is to find such activity in the organism if a rigorous definition is used i.e., activity arising *within* cells. Three examples from experimental work in progress at the Wilmer laboratories are discussed. (1) "Spontaneous" maintained nervous action in the unopened circulated mammalian eye, cut off from all extraneous light stimuli. (2) Activity at the pacemaker regions of the frog heart. The time course and location of pacemaker processes by intracellular recording methods is illustrated in addition to nervous control mechanisms by the vagus and sympathicus. (3) Activity in isolated nerve cells from crustacea is shown to be analogous to that in the heart pacemaker regions. The similarities are particularly striking between inhibitory mechanisms and the graded processes leading to conducted impulses.

CLINICAL AND LABORATORY OBSERVATIONS ON THE TREATMENT OF COMPLETE HEART BLOCK

SAMUEL H. BOYER IV AND JOHN F. MURRAY[1]

Molar sodium lactate has been described as a safe and effective agent in the treatment of bradycardia accompanying complete heart block (1). Twelve patients with heart block and bradycardia or asystole were given half or one molar sodium lactate on twenty-two occasions. Contrary to previous reports, hypertonic sodium lactate was found to be much less efficacious and far more hazardous than isopropylnorepinephrine. Lactate infusion produced increased frequency of ectopic beats in seven patients of whom six developed ventricular tachycardia on ten occasions. Many of these latter patients had slowing of idioventricular rate before the appearance of tachycardia. Only four patients on six occasions had an increase in ventricular rate without developing ectopic beats. Several patients exhibited totally different responses on different occasions. Isopropylnorepinephrine, given sublingually to nine of the twelve patients studied, did not produce ectopic beats and was consistently followed by increased ventricular rate in six patients.

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The effects of hypertonic sodium bicarbonate were compared with the results of lactate infusions in a few patients. The greater magnitude of ventricular rate increase after lactate suggests that its rapid uptake and utilization by the myocardium promotes greater myocardial alkalosis and irritability. Rapid change in alkalinity of extracellular fluid is suggested as another factor in increasing rate and perhaps promoting automaticity and irritability of ectopic foci.

Preliminary results of studies in animals with surgically induced heart block indicate that intravenously administered isopropylnorepinephrine is many times more effective in increasing ventricular rate than l-norepinephrine which in turn is slightly more effective than l-epinephrine. Molar lactate infusions have little effect on ventricular rate except under conditions of severe hypoxia at which time the rate increases without development of ectopic beats. Under similar circumstances as well as during prolonged mild hypoxia, the three named sympathicomimetic drugs often produce numerous ectopic beats or ventricular tachycardia. In well oxygenated dogs far fewer ectopic beats appeared after these agents.

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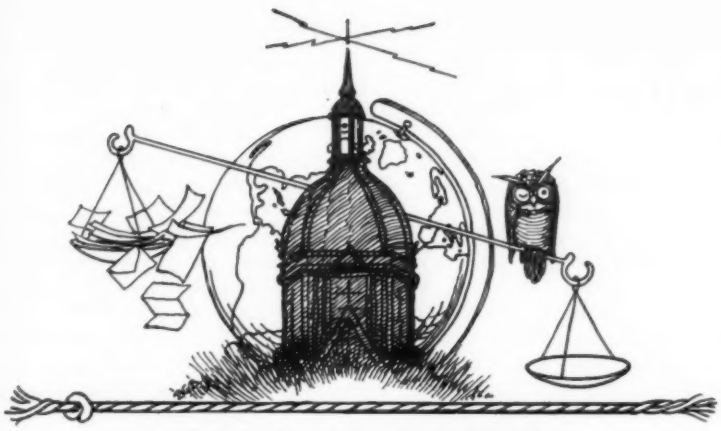

BOOK REVIEWS

Heritable Disorders of Connective Tissue. By VICTOR A. MCKUSICK. 224 pp., $7.50. The C. V. Mosby Co., St. Louis, Missouri.

The art of philosophy has been defined as the ability to see the remarkable in daily things and the commonplace in the unusual happenings. This little volume, in which Dr. McKusick has enthusiastically collected a number of the rarer and genetically conditioned disorders of connective tissue, is a concrete application of this art. Heritability of recessive defects and the bald fact that the defects involve the binding material of the body elect them to a level of basic importance. Yet the diseases themselves are sufficiently rare to become "collector's items", so each example has to be pored over, considered from all aspects and arbitrary taxonomic decisions taken. Dr. McKusick's presentation, however, reminds us they all may present some one unknown defect in the way collagen is put together. Recent electron microscopic studies have shown the complicated structure of this fibrous protein, and there is constant temptation to suppose that it is at the sub-microscopic level that the defect exists. However, tentative attempts in this direction have so far failed. Perhaps with increasing knowledge of how, when, and where the connective tissue is breaking down some one will find the key to the process. This monograph contributes to this knowledge. The book includes a full discussion of the Marfan syndrome, the Ehler-Danlos syndrome, Osteogenesis Imperfecta, Pseudoxanthoma Elasticum, the Hurler syndrome, and a discourse on Fibrodysplasia Ossificans Progressiva, Osteopoikilosis, Leri's pleonosteosis, Paget's disease of bone—and a few other rarities. Those who may be confused will find helpful footnotes such as the one for osteopetrosis (Albers-Schönberg's disease)*:

> "*Albers-Schönberg was one man; this is not a syndrome named for two persons like the Ehlers-Danlos syndrome or the Grönblad-Strandberg syndrome. Care should be taken not to confuse osteopetrosis with osteopoikilosis which was also first described in a definitive manner by Albers-Schönberg; some writers have evidenced this confusion".

The major contribution of this book seems to this reviewer to be the careful sifting of data from many case reports, clinical descriptions and personal studies, so that pictures of the syndromes emerge more sharply, and in turn the role of heredity is more clearly defined.

F. B. BANG

Pediatrics. Edited by DONALD PATERSON AND JOHN FERGUSON MCCREARY. 654 pp., $14.00. J. B. Lippincott Co., Philadelphia, Pa.

This text has been compiled from the contributions of a large group of outstanding Canadian pediatric authorities. It is edited for use primarily by practitioners caring for children and is not intended as a reference book for specialized aspects of child care. The material is arranged in the conventional fashion with discussions of diseases by systems but preceded by introductory chapters on routines for diagnostic study of pediatric patients as well as the usual chapters on physical, emotional and social growth and development. There is a short section on diagnosis and management of symptoms which are peculiar to diseases of infants but no attempt to give complete differential diagnosis is intended. The text is admittedly restricted to problems commonly encountered in the practice of pediatrics. There is some mention made of rare disease entities but the discussion of these topics is understandably brief in order to limit the size of the textbook. There are certain sections which are particularly good in relation to other textbooks in pediatrics now available. These include discussions on pediatric gynecology, pediatric ophthalmology, pediatric orthopedics as well as an excellent section on the management of retarded children which includes excellent suggestions for help to parents of these children. In addition a bibliography is supplied for parents of such children. Some of the discussions of disease, however, are inadequate with omission of important material in several of the chapters. The tables and figures are poorly annotated and frequently are not referred to in the text. The casual reader may find these tables and figures of little value as a consequence. The bibliography which is well chosen and current is one of the better features of the text. The text should be of considerable value to practitioners, particularly in Canada and Great Britain. Students in medical schools in this country and Canada should probably require texts with more basic science information in relation to the care of children than is included in this text.

ROBERT E. COOKE

Endogenous Uveitis. By ALAN C. WOODS. 303 pp., $12.50. The Williams & Wilkins Co., Baltimore, Md.

This book is the outgrowth of a teaching manual first published in 1948 by the American Academy of Ophthalmology and Otolaryngology as a part of its home-study courses. The subject of endogenous uveitis has been presented under the general headings of nomenclature, classification, pathogenesis, symptomatology, diagnosis and treatment. The material is brilliantly organized and clearly presented. There are numerous photomicrographs demonstrating the histology of various types of endogenous uveitis. Forty-two colored plates, including 34 drawings by Annette Smith Burgess, complement the text. This book should be read by every student of ophthalmology and by every trained ophthalmologist.

H. A. N.

BOOKS RECEIVED FOR REVIEW

Clinical Orthopaedics No. 8. Edited by ANTHONY F. DE PALMA. 337 pp., $7.50. J. B. Lippincott Co., Philadelphia, Pa.

The Happy Life of a Doctor. By ROGER I. LEE. 278 pp., $4.00. Little, Brown & Co., Boston, Mass.

Heart Sounds, Cardiac Pulsations, and Coronary Disease. By WILLIAM DOCK. 98 pp., $2.50. University of Kansas Press, Lawrence, Kansas.

History of the American Board of Surgery 1937–1952. By J. STEWART RODMAN. 104 pp., $3.00. J. B. Lippincott Co., Philadelphia, Pa.

Low-Fat Cookery. By EVELYN S. STEAD AND GLORIA K. WARREN. With an introduction by Eugene A. Stead, Jr. and James V. Warren. 184 pp., $4.95. McGraw-Hill Book Co., New York, N. Y.

Lymphatics, Lymph and Lymphoid Tissue, 2nd edition. By JOSEPH MENDEL YOFFEY AND FREDERICK COLIN COURTICE. 510 pp., $10.00. Harvard University Press, Cambridge, Mass.

Progress in Nuclear Energy. Series Six. Vol. I, Biological Sciences. Edited by J. C. BUGHER, J. COURSAGET AND J. F. LOUTIT. 205 pp., $7.00. McGraw-Hill Book Co., New York, N. Y.